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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,360	05/09/2005	Masanori Nakasu	P27827	4868

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EXAMINER	
NOBLE, MARCIA STEPHENS	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/534,360	NAKASU ET AL.	
	Examiner	Art Unit	
	Marcia S. Noble	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-16 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-16 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 8/16/2005.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-16 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The instant invention is drawn to an osteogenic treatment device, comprising a nucleic acid containing a base sequence coding for BMP protein and a base sequence derived from an expression plasmid; an angiogenesis factor; a non-viral vector for holding the nucleic acid; and a biocompatible base body being constructed from a porous block body having interconnected holes in which the adjacent communicate with each other; wherein the angiogenesis factor is mixed with the nucleic acid, in which the mixing ratio between the angiogenesis factor and the nucleic acid id in the range of about 10:1 to 1:100 by weight, and wherein in a case where the are (average) of the holes is defined as A and the maximum cross-sectional area (average) of the holes is defined as B, the value of B/A is in the range of 2 to 150.

The specification describes the main objective of the instant invention as being, "to provide an osteogenic treatment device having an excellent bone forming ability." (p. 3, par 4, lines 2-4). However, by disclosing broadly "an osteogenic treatment device" with the subsequent broad parameters as described above in the preceding paragraph, the instant invention encompasses a much broader range of inventions that the disclosed objective of the present invention. For example, an osteogenic treatment device may also include factors for breaking down bone and reducing bone vascularity

that maybe associated with treating some bone malformations, dysplasias, and angio-osteohypotrophic syndromes, such as Haemodynamic pathogenesis and arthritic induced hyperoseotosis. The specification only discusses the instant invention in terms of bone growth and therefore does not support the broader embodiments encompassed in the device for osteogenic treatment. Given the brief the instantly claimed invention, the specification does not support all potential embodiments of the claimed invention therefore not enabling an artisan to use or make all aspects of the instantly claimed invention.

The instant invention also encompasses "a nucleic acid containing a base sequence coding for BMP protein and a base sequence derived from an expression plasmid". The breadth of this statement suggests that this can be any nucleic acid sequence that encompasses the coding sequence for a BMP protein. From a functional standpoint, not just any sequence containing a coding sequence for BMP will be able to result in the production of BMP protein with the desired activity of promoting bone growth within the implant. A functional expression vector for a gene therapy is reliant upon a promoter that is capable of driving the expression of the gene in target cells and the success of such treatment is reliant upon the specificity and strength of that promoter to reliably drive expression (Tomason and Benigni Current Gene Therapy 4:115, col 1, lines 4-7.) Furthermore, successful treatment with growth factors, such as BMP, are heavily reliant upon time dosage and cellular content (Carano and Filvaroff et al., Drug Disc Today 8(21):982, col 2, par 1, lines 1-3, 2003). At the time of filing and presently, the ability to deliver a gene product consistently, constitutively, or with any

timing and dosage requirements is relatively beyond the capability of gene therapies or are unpredictable at least (Franceschi et al. Cells Tissues Organs 176: 104, par bridging col 1 and 2, 2004). Overall, in any gene therapy, the specifics of its construct describing the elements targeting that vector to a specific cell and driving specific expression of a gene are crucial to enable its make and use by an artisan. The instant invention includes a base sequence derived from an expression plasmid. This may encompass such a promoter and it would also encompass nonfunctional nucleotides present at the end of a restriction site used to excise and isolate a sequence that encompasses the coding sequence for a BMP protein. Given the crucial nature of the gene construct to the success of any gene therapy, the broad claim to "a nucleic acid containing a base sequence coding for BMP protein and a base sequence derived from an expression plasmid" does not provide enough guidance to enable to instant invention. Furthermore, the specification does not provide any examples of a nucleic acid containing a base sequence coding for BMP protein and a base sequence derived from an expression plasmid that could sucessfully be used in the instant invention, therefore the artisan could not derived meaning from the specification of such matters.

The instant osteogenic treatment device is encompasses the treatment with the osteogenic family of factors BMP. A narrowing embodiment specifies the use of BMP-2, -4, or –7. The art supports BMPS as osteogenic factors. However, treatment with one osteogenic factor underestimates the complexity of the various interactions of BMPs with other BMPs and other osteogenic factors that work in concert to promote osteogenesis. Franceschi et al teach the limitation of a gene therapy with a single

osteogenic factor in bone reconstruction. "This approach has several limitations. (1) Because only a single factor is expressed at a time, it fails to adequately mimic normal processes of bone development and fracture healing where multiple secreted factors function in a cooperative and/or sequential fashion to regulate the osteogenic response...(2) It is essentially uncontrolled, being limited only by the in vivo half-life of the vector and target cells at the implantation site. (3) It is focused exclusively on the use of soluble factors, yet the osteogenic activity of bone progenitors can also ve enhanced by induction of intracellular components such as transcription factor..." (p. 104 par bridging col 1 and 2). In more specific reference to BMP, Franceschi et al teaches that the various BMPs work synergistically in bone formation. "Although homodimers of BMPs 2, 4, and 7 can induce ectopic bone formation, there is strong evidence that these factors act in combination. For example, BMPs 2, 4, and 7 are coexpressed during development and fracture healing and may exist as heterodimers...Furthermore, BMP2/7 and 4/7 heterodimers have greater biological activity than homodimers when assayed for their ability to induce ventral mesoderm and blood in Xenopus animal caps..." (p. 104, col 2 par 2).

To some extent, the specification and instant invention acknowledges the complexity of the osteogenic factors involved in bone generation by the instant invention necessitating an angiogenic factor be present as a component of the device. The specification teaches that an angiogenic factor needs to be present to promote blood vessels formation to support osteoblast differentiation (p. 5, par 2, lines 4-7). This adds another level of complexity to the treatment device and bone regeneration. There are a

multitude of angiogenic factors involved in angiogenesis and bone generation that an artisan could be overwhelmed by the possibilities for treatment. The instant invention contains narrowing embodiments that specify the use of bFGF, VEGF, or HGF. Because vascular formation is inextricable intertwined with the process of bone generation, many of the angiogenic factors function as osteogenic factors as well. Carano and Filvaroff teach that bFGF and VEGF play a significant role in skeletal development and bone repair as well as serving as an angiogenic agentic (p. 981 col 1, par 3). For example, VEGF, a major known player in angiogenesis, increases osteoblast chemotaxis, proliferation, and differentiation (p. 983, col 1, lines 8-13). VEGF is also known to interact with BMP-4 to enhance bone formation (p. 982 col 2, par 2, lines 16-20).

Overall, the instant device use of a BMP and an angiogenic has complex implications for the functioning of this instant invent and therefore the use and make of the instant invention. An artisan would have to rely heavily upon the art to determine what combination of BMP and angiogenic factor even including the narrowing embodiments to determine what BMP and angiogenic factor to use to generate bone formations, because the specification only discuss these factors very broadly and does not discuss some of the complexities of the interaction that would need to be considered. Furthermore, an artisan may very well have to try various combinations and then optimize the device before use, this level of experimentation is considered undue and therefore not enabling of the instant osteogenic device.

The instant invention further specifies the angiogenesis factor is mixed with the nucleic acid, in which the mixing ratio between the angiogenesis factor and the nucleic acid id in the range of about 10:1 to 1:100 by weight. This embodiment of the claims, as written is independent of the biocompatible base body being constructed from a porous block body having interconnected holes in which the adjacent communicate with each other. Nowhere in the specification does it teach how the mixture is to interact with the biocompatible base body of the instant invention. Therefore and artisan would not know how to make or therefore use the instant invention. Furthermore, the specification does not teach what a base body, a porous block body, or how the adjacent holes communicate to each other. In general, holes do not communication to each other in biological system, so an artisan would not know how to make a porous device wherein the holes communicate to each other. It may be that applicant is referring to cell the can interact, but if this is the case, an artisan could not discern what cells.

The instant invention also specifies "a non-viral vector for holding the nucleic acid". In narrowing embodiments they specify the nonviral vector includes a cationic liposome. In broad interpretations of this claims a nonviral vector can encompass the nucleic acid sequence itself or the body base. The specific use of a cationic liposome has been used in bone gene therapy, but, like in other applications of gene therapy, liposomes are unpredictable in their efficacy to deliver constructs. Franeschi et al states, "Although recent advances involving condensation of DNA with liposome and other carriers have the potential to enhance the uptake of nonviral DNA by cells, currently the efficiency of this process is approximately 10^{-9} that of viral vectors." (p. 97

col 1 par 2, lines 12-19). This level of inefficiency can lead to low expression and may not be able to result in a therapeutic dose delivery. The specification acknowledges that large doses of BMP would need to be delivered to the cite of regeneration, and given the liposomal delivery efficiency is unpredictable, it would not be clear to an artisan that liposomal delivery would effectively deliver a therapeutically effective dose of the gene. Therefore an artisan would not necessarily be able to make or use the instant invention.

The instant invention is drawn to "a base body" and a "block body", but nowhere in the specification are a base body or block body and their relationship to each other defined. From reviewing the art, these terms seem to be their own terminology and a further understanding of them could not be gleamed from the art. Given that neither the art or the specification provided enough guidance to discern a base or block body, and artisan would not know how to use or make the instant invention.

Overall, due to the breadth of the claims and the lack of specific guidance by the specification, an artisan would not be enable to use of make the instant inventions, therefore the instant invention is not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-16 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and 16 specifically recite "a base sequence derived from an expression plasmid". The metes and bound of a "base sequence" is not clear. Does base sequence sole refer to a nucleic acid sequence, a fragment of the nucleic acid sequence that is common among all the BMPs, or a sequences for one particular BMP?

The metes and bounds of "derived" is also considered vague and indefinite. Derive can have a broad range of interpretations.

Derive: To obtain or receive from a source.

1. To arrive at by reasoning; deduce or infer: *derive a conclusion from facts.*
2. To trace the origin or development of (a word).
3. *Linguistics.* To generate (a surface structure) from a deep structure.
4. *Chemistry.* To produce or obtain (a compound) from another substance by chemical reaction.

<http://dictionary.reference.com/search?q=derived>

Given the breadth of the definition of "derived", the metes and bounds of a differentiated cell line "derived" from one of the various claimed cell lines are unclear.

The clause, "a base sequence derived from an expression plasmid" is vague and indefinite because it essentially encompasses any nucleic acid sequences. Therefore the metes and bound are undefined.

Furthermore, the dependent claims fail to clarify the basis of the rejection.

4. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 16 specifically recite " a non-viral vector holding the nucleic acid". The metes and bound of this phrase are unclear. It is unclear to what or how the vector "holds" the nucleic acid.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-8 and 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP2001-505097 (translation of record), JP2000-302567 (translation of record) and Street et al. (PNAS 99(15):9656-9661, July 2002).

The instant invention is drawn to an osteogenic treatment device, comprising a nucleic acid containing a base sequence coding for BMP protein and a base sequence derived from an expression plasmid; an angiogenesis factor; a non-viral vector for holding the nucleic acid; and a biocompatible base body being constructed from a porous block body having interconnected holes in which the adjacent communicate with each other; wherein the angiogenesis factor is mixed with the nucleic acid, in which the mixing ratio between the angiogenesis factor and the nucleic acid id in the range of about 10:1 to 1:100 by weight, and wherein in a case where the are (average) of the holes is defined as A and the maximum cross-sectional area (average) of the holes is defined as B, the value of B/A is in the range of 2 to 150.

JP2001-505097 teaches an osteogenic treatment device comprising a DNA encoding a protein of osteogenesis, more specifically a BMP family member and a biodegradable porous matrix containing tricalcium phosphate ceramics with continuous micropores in the volume range of 20-60%. It also teaches a mixtures with other proteins for osteogenesis (p. 4 lines 13-18). It also teaches any suitable expression vector (p. 4 line 32). It does not teach specifically an angiogenic factor and the specific dimensions and properties of the instant invention.

JP2000-302567 teaches a sintered compact that is made of porous calcium phosphate with a porosity of 55 to 90% with spherical pores that communicate with one

another. The average diameter of the communicating parts between the pored is not less than 50 .m and the pores diameters are not less than 150 .m. It also teaches the use for bone implants or replacements structures. JP2000-302567 does not teach the use with gene therapy.

Street et al teach that the angiogenic factor are also osteogenic factors and therefore the two processes of angiogenesis in bone formation and generation of bone itself are inextricably linked. Though inhibition of VEGF in a bone healing model, Street et al teach that VEGF inhibition impaired bone repair through disruption of osteoblast differentiation (p. 9656, col 2 lines 7-14). Their studies also reaffirm the importance of VEGF as an angiogenic factor in early angiogenesis in bone repair col 2, par 1). They also provide evidence that VEGF activity is essential for appropriate callus formation and mineralization in response to bone injury (p9659 par bridging col 1 and 2). They also teach that angiogenic factors bFGF and BMP family involvement in bone repair and promote blood vessel formation. bFGF promotes osteoblast proliferation and augment fracture healing. VEGF has been shown to modulate bFGF and BMP-2 angiogenic activity (p9661, par bridging col 1 and 2). These finding suggest that BMP family of gene could serve both the osteogenic and angiogenic limiations of the instant invention. Street et al also provides motivation for the use of VEGF in a therapy as being its involvement in coupling angiogenesis with bone formation and remodeling (p. 9661 Line bridging col 1 and 2). Street et al does not teach specific use in a device for osteogenic treatment nor does it teach a biocompatible body base with a the specific defining characteristics.

The embodiments of the ratio of protein mixture and a biocompatible base body would be obvious to one of ordinary skill in the art preparing device. An artisan would know that these parameters are dependent on the materials being use to produce the base body and also the BMP construct and the level of expression it provides as well as the properties of angiogenic factor being used in the mixture.

At the time of the invention, it would have been obvious to an artisan of ordinary skill to modify the knowledge and methods of JP2001-505097, JP2000-302567 (translation of record) and the information provided by Street et al. Street et al also provides motivation provide the motivations for the to consider the use of VEGF or BMP for it multipotent abilities in angiogenesis and osteogenesis. Furthermore, it also would have been obvious to an artisan of ordinary skill to use VEGF or BMP protein in the mixture with a reasonable expectation of success because they have been both used effectively in treatments independently.

6. Claims 1-8 and 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat Ap 2002/0082694 A1, JP2000-302567 (translation of record) and Street et al. (PNAS 99(15):9656-9661, July 2002).

The instant invention is drawn to an osteogenic treatment device, comprising a nucleic acid containing a base sequence coding for BMP protein and a base sequence derived from an expression plasmid; an angiogenesis factor; a non-viral vector for holding the nucleic acid; and a biocompatible base body being constructed from a porous block body having interconnected holes in which the adjacent communicate with

each other; wherein the angiogenesis factor is mixed with the nucleic acid, in which the mixing ratio between the angiogenesis factor and the nucleic acid id in the range of about 10:1 to 1:100 by weight, and wherein in a case where the are (average) of the holes is defined as A and the maximum cross-sectional area (average) of the holes is defined as B, the value of B/A is in the range of 2 to 150.

US Pat Ap 2002/0082694 A1 teaches an osteogenic treatment device comprising a DNA encoding a protein of osteogenesis, more specifically a BMP family member and a biodegradable porous matrix containing tricalcium phosphate ceramics or hydroxiapetite dispersed into a collagen slurry as described in the instant specification [0021], [0025], [0007] & [0020]. It also teaches a mixtures with other proteins that are osteogenic enhancing factors [0028]. It does not teach specifically an angiogenic factor and the specific dimensions and properties of the instant invention.

JP2000-302567 teaches a sintered compact that is made of porous calcium phosphate with a porosity of 55 to 90% with spherical pores that communicate with one another. The average diameter of the communicating parts between the pored is not less than 50 .m and the pores diameters are not less than 150 .m. It also teaches the use for bone implants or replacements structures. JP2000-302567 does not teach the use with gene therapy.

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differentiation (p. 9656, col 2 lines 7-14). Their studies also reaffirm the importance of VEGF as an angiogenic factor in early angiogenesis in bone repair col 2, par 1). They also provide evidence that VEGF activity is essential for appropriate callus formation and mineralization in response to bone injury (p9659 par bridging col 1 and 2). They also teach that angiogenic factors bFGF and BMP family involvement in bone repair and promote blood vessel formation. bFGF promotes osteoblast proliferation and augment fracture healing. VEGF has been shown to modulate bFGF and BMP-2 angiogenic activity (p9661, par bridging col 1 and 2). These finding suggest that BMP family of gene could serve both the osteogenic and angiogenic limitations of the instant invention. Street et al also provides motivation for the use of VEGF in a therapy as being its involvement in coupling angiogenesis with bone formation and remodeling (p. 9661 Line bridging col 1 and 2). Street et al does not teach specific use in a device for osteogenic treatment nor does it teach a biocompatible body base with a the specific defining characteristics.

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At the time of the invention, it would have been obvious to an artisan of ordinary skill to modify the knowledge and methods of US Pat Ap 2002/0082694 A1, JP2000-302567 (translation of record) and the information provided by Street et al. Street et al

also provides motivation provide the motivations for the to consider the use of VEGF or BMP for it multipotent abilities in angiogenesis and osteogenesis. Furthermore, it also would have been obvious to an artisan of ordinary skill to use VEGF or BMP protein in the mixture with a reasonable expectation of success because they have been both used effectively in treatments independently.

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marcia S. Noble